

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 2

In the claims:

Please replace the claims with the listing of claims below.

1. (currently amended) An isolated regulatory peptide ~~comprising~~ consisting of an amino acid sequence as denoted by SEQ ID NO: 1, wherein said peptide promotes cell growth or cell differentiation or both, and wherein said peptide corresponds to the C-terminal region of the readthrough variant of acetylcholinesterase.
2. (currently amended) A synthetic peptide ~~comprising~~ consisting of the amino acid sequence as denoted by SEQ ID NO: 1.
3. (currently amended) The ~~isolated~~ peptide according to any one of claims 1 and 2, ~~having~~ consisting of the amino acid sequence as denoted by SEQ ID NO: 1.
4. (cancelled)
5. (currently amended) ~~The isolated~~ A synthetic peptide ~~according to claim 3, which~~ consisting of the amino acid sequence as denoted by SEQ ID NO:1, which peptide promotes cell growth or cell differentiation or both, and corresponds to the C-terminal region of the readthrough variant of acetylcholinesterase, wherein said peptide is linear.
6. (currently amended) ~~The isolated~~ A synthetic peptide ~~according to claim 3, which~~ consisting of the amino acid sequence as denoted by SEQ ID NO:1, which peptide promotes cell growth or cell differentiation or both, and

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 3

corresponds to the C-terminal region of the readthrough variant of acetylcholinesterase, wherein said peptide is cyclic.

7. (currently amended) The ~~isolated~~ peptide according to any one of claims 1 to 3, wherein said peptide promotes cell survival.
8. (currently amended) The ~~isolated~~ peptide according to any one of claims 1 to 3, which is any one of hematopoietic stem cell growth peptide and differentiation regulatory peptide.
9. (currently amended) The ~~isolated~~ peptide according to claim 7, wherein said peptide promotes stem cell survival or myeloid and megakaryocytic differentiation, or both.
10. (currently amended) The ~~isolated~~ peptide according to claim 7, wherein said peptide promotes endothelial cell growth.
11. (withdrawn) A method of *ex vivo* and *in vivo* expansion of hematopoietic stem cells, comprising contacting said cells with the regulatory peptide according to claim 7.
12. (withdrawn) The method according to claim 10, wherein said regulatory peptide has the amino acid sequence as denoted by SEQ ID NO:1.
13. (withdrawn) A method for promotion of *ex vivo* and *in vivo* promotion of megakaryocytic differentiation of hematopoietic stem cells, comprising contacting said

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 4

cells with the peptide according to any one of claims 6 and 7.

14. (withdrawn) The method according to claim 12, wherein said peptide has the amino acid sequence as denoted by SEQ ID NO:1.
15. (withdrawn) A method for promoting stem cell survival and/or myeloid and/or megakaryocytic differentiation, comprising contacting said cells with the peptide according to claim 8.
16. (withdrawn) A method for promoting endothelial cell growth, comprising contacting stem cells with the peptide according to claim 9.
17. (withdrawn) A method for *ex vivo* and *in vivo* expansion of hematopoietic stem cells, comprising contacting said cells with the peptide according to claim 7.
18. (withdrawn) Use of a peptide comprising the amino acid sequence denoted by SEQ ID: No. 1 in the regulation of hematopoietic stem cell growth.
19. (withdrawn) Use according to claim 18, in promoting survival of stem cells.
20. (withdrawn) Use according to claim 18, in promoting differentiation of stem cells.
21. (withdrawn) Use according to claim 18, in promoting growth of stem cells.

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 5

22. (withdrawn) Use according to claim 18, in promoting the growth-enhancing effect of a growth factor on stem cells.
23. (withdrawn) Use according to claim 18, in promoting the growth-enhancing effect of GM-CSF, SCF, or TPO on stem cells.
24. (withdrawn) Use according to any one of claims 20 and 21, wherein the stem cells are embryonic stem cells.
25. (withdrawn) Use according to any one of claims 20 and 21, wherein the stem cells are epithelial stem cells.
26. (withdrawn) Use according to any one of claims 20 and 21, wherein the stem cells are mesenchymal stem cells.
27. (withdrawn) Use according to any of claims 20 and 21, wherein the stem cells are hematopoietic stem cells.
28. (withdrawn) Use of a peptide according to claims 1 to 9 and 11 to 13, in the preparation of a pharmaceutical composition for the treatment of at least one of thrombocytopenia, post-irradiation conditions, post-chemotherapy conditions, and conditions following massive blood loss.
29. (withdrawn) Use of a peptide according to claims 1 to 9, in inducing synthesis of acetylcholinesterase mRNA.
30. (withdrawn) Use according to claim 18, promoting the formation of hematon bodies.

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 6

31. (withdrawn) An antibody directed against a peptide of claims 1 to 10, for use in diagnosing at least one of elevated glucocorticoid level; bone marrow stress, abnormality, dysfunction, and stressed condition, of one of increased platelet count and of brain infarct risk in a mammal.
32. (withdrawn) An antibody directed against the ARP peptide as denoted by SEQ ID NO:1, which antibody is specific for any one of the AChE-R variant of acetylcholinesterase and a C-terminal peptide derived therefrom.
33. (withdrawn) The antibody according to claim 32, for use in diagnosing stress-induced male infertility.
34. (withdrawn) A method for the diagnosis of at least one of elevated glucocorticoid level, bone marrow stress, abnormality, dysfunction and stressed condition, of one of increased platelet count and of brain infarct risk in a mammal, comprising obtaining a sample from said mammal, contacting said sample with an antibody of claim 32, removing unbound antibody, and detecting the extent of reaction between said antibody and acetylcholinesterase or a fragment thereof present in said sample, whereby the presence of AChE-R in said sample indicates the existence of at least one of elevated glucocorticoid level, bone marrow stress, abnormality, dysfunction and stressed condition, of one of increased platelet count and of brain infarct risk in said mammal.

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 7

35. (withdrawn) A method according to claim 34 wherein said sample is a serum or bone marrow sample.
36. (withdrawn) A method for the diagnosis of stress-induced male infertility comprising obtaining a sperm cell sample from said male; smearing and drying said sample; contacting said dried sample with an antibody specific for the AChE-R variant of acetylcholinesterase according to claim 32; removing unbound antibody; detecting the extent of reaction between said antibody and the AChE-R variant of acetylcholinesterase or a fragment thereof present in said sample; determining the pattern of expression of the AChE-R variant of acetylcholinesterase or a fragment thereof, in said sperm cells; whereby the absence of AChE-R from sperm heads together with intense presence in the midpiece region indicates the presence of stress-induced male infertility.
37. (withdrawn) A method according to claim 36, for use in fertility consulting.
38. (withdrawn) A method for the screening of candidate drugs that affect central nervous system, wherein said drug is a modulator of an interaction between AChE-R/RACK1/PKC, which screening method comprises the steps of:
- a. providing a reaction mixture comprising the AChE-R variant of AChE or any functional fragment thereof, the cognate receptor for activated kinase C (RACK1) and the protein kinase C  $\beta$ II (PKC $\beta$ II);
  - b. contacting said mixture with a test drug under suitable conditions for said interaction; and

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 8

- c. determining the effect of the test drug on an end-point indication, wherein said effect is indicative of modulation of said interaction by the test drug.
39. (withdrawn) The method according to claim 38, wherein said modulator inhibits or enhances the interaction between AChE-R/RACK1/PKC.
40. (withdrawn) The method according to claim 38, wherein said reaction mixture is a cell mixture or a cell-free mixture.
41. (withdrawn) The method according to claim 40, wherein said reaction mixture optionally further comprises solutions, buffers and compounds which provide suitable conditions for interaction between AChE-R/RACK1/PKC and the detection of an end-point indication for said interaction.
42. (withdrawn) The method according to claim 38, wherein modification of said end-point indicates modulation of the interaction between AChE-R/RACK1/PKC by said test drug.
43. (withdrawn) The method of claim 40, wherein the reaction mixture is a cell-free mixture.
44. (withdrawn) The method according to claim 43, wherein said screening method comprises the steps of:
- a. providing a cell free mixture comprising the AChE-R variant of AChE or any functional fragment thereof, RACK1 and PKC $\beta$ II;

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 9

- b. contacting said mixture with a test drug under conditions suitable for an *in vitro* interaction; and
  - c. determining the effect of the test drug on co-precipitation of PKC $\beta$ II and RACK1 with the AChE-R or fragment thereof as an end-point indication, whereby the absence or increase of said co-precipitation indicates modulation of formation of a complex between AChE-R/RACK1/PKC by the test drug.
45. (withdrawn) The method according to claim 44, wherein said cell-free mixture comprises any one of AChE-R variant of AChE or any functional fragment thereof, RACK1 and PKC $\beta$ II, which are provided as purified recombinant protein or as a cell lysate from cells expressing said proteins.
46. (withdrawn) The method according to claim 45, wherein said AChE-R variant of AChE is a fusion protein comprising AChE-R or functional fragment thereof and any one of GST (Glutathion-S-Transferase) and GFP (Green Fluorescent Protein).
47. (withdrawn) The method according to claim 38, wherein said reaction mixture is a cell mixture.
48. (withdrawn) The method according to claim 47, wherein said cell mixture is a transfected cell culture.
49. (withdrawn) The method according to claim 48, wherein said screening method comprises the steps of:



Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 10

- a. providing a transfected cell culture expressing the AChE-R variant of AChE or functional fragment thereof, the cognate receptor for activated kinase C (RACK1) and the PKC $\beta$ II;
  - b. contacting said transfected cell culture with a test substance;
  - c. detecting the interaction between AChE-R/RACK1/PKC in the presence of the test substance/drug by searching for an end-point indication, whereby inhibition of said end-point indicates inhibition of complex formation between AChE-R/RACK1/PKC by said test drug.
50. (withdrawn) The method according to claim 49, wherein said transfected cell is transfected by:
- a. an expression vector comprising a nucleotide sequence coding for the AChE-R variant of AChE or a functional fragment thereof;
  - b. optionally, constructs comprising a nucleic acid sequence coding for any one of the cognate receptor for activated kinase C (RACK1) and the PKC $\beta$ II.
51. (withdrawn) The method according to claim 50, wherein the end-point indication is the subcellular translocation of catalytically active PKC $\beta$ II, which can be detected by a visually detectable signal.
52. (withdrawn) The method according to claim 44, wherein the end-point indication is co-precipitation of PKC $\beta$ II and RACK1 with the AChE-R or functional fragment thereof leading to a detectable signal, whereby modification of said detectable signal in the presence of the test drug

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 11

indicates modulation of the formation of a complex between AChE-R/RACK1/PKC by said test drug.

53. (withdrawn) The method according to any one of claims 49 to 51, wherein said transfected cell is a mammalian cell.
54. (withdrawn) The method according to any one of claims 38 to 49, wherein said test drug is selected from the group consisting of protein based, carbohydrates based, lipid based, nucleic acid based, natural organic based, synthetically derived organic based, antibody based and metal based substances.
55. (withdrawn) The method according to claim 54, wherein said protein or antibody based substance is a product of a combinatorial library.
56. (withdrawn) The method according to any one of claims 38 to 55, wherein the modulator of the interaction between AChE-R/RACK1/PKC also modulates the expression and subcellular distribution of RACK1.
57. (withdrawn) The method according to any one of claims 38 to 55, wherein the modulator of the interaction between AChE-R/RACK1/PKC also modulates the expression of PKC $\beta$ II.
58. (withdrawn) A method for the *in vivo* screening of candidate drugs aimed at affecting central nervous system properties, wherein said drug is a modulator of an interaction between AChE-R/RACK1/PKC, which screening method comprises the steps of:
- a. providing an AChE-R transgenic animal;

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 12

- b. administering the test drug to said animal;
  - c. sacrificing the animal and dissecting its brain to give samples for preparation of brain extracts or for immunohistochemistry;
  - d. detecting the expression of RACK1 or PKC $\beta$ II in said brain samples;
  - e. determining the effect of the test drug on an end-point indication, wherein said effect is indicative of the *in vivo* modulation of said interaction by the test drug.
59. (withdrawn) The method according to claim 58, wherein said end-point indication is the expression of RACK1 and PKC $\beta$ II in the brain, which can be detected by a visually detectable signal.
60. (withdrawn) The method of claim 59, wherein the expression of RACK1 or PKC $\beta$ II is detected by means that can detect RNA or protein.
61. (withdrawn) The method of claim 60, wherein said RNA detection is performed by means appropriate for RNA detection, said means selected from the group consisting of RT-PCR, Northern Blot, *in situ* hybridization, RNase protection and S1 nuclease analysis.
62. (withdrawn) The method of claim 60, wherein said protein detection is performed by means appropriate for protein detection, said means selected from the group consisting of Western Blot and immunohistochemistry.

Applicants: Hermona Soreq et al.  
Serial No.: 09/998,042  
Filed: November 30, 2001  
Page 13

63. (withdrawn) The method according to any one of claims 38 to 62, wherein said test drug is selected from the group of drugs for the treatment of anxiety conditions, post-traumatic stress, Alzheimer's disease, muscle malfunctioning, neurodegenerative disorders, damage resulting from exposure to xenobiotics, panic, neuromuscular disorders, Parkinson's disease, Huntington's chorea, muscle fatigue, multiple chemical sensitivity, autism, multiple sclerosis and Shorgren's disease.
64. (withdrawn) A method for the treatment of stress-associated conditions or disorders, for a subject in need of such treatment, comprising:
- a. providing a composition comprising as active ingredient a modulator of an interaction between AChE-R/RACK1/PKC;
  - b. administering a therapeutic effective amount of said composition to said subject.
65. (withdrawn) The method according to claim 64, wherein said modulator is selected by the method of any one of claims 38 to 62.